APPLICATION OF FIXED EXPONENT 0.75 TO THE PREDICTION OF HUMAN DRUG CLEARANCE: AN INACCURATE AND MISLEADING CONCEPT

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SUMMARY

Considering the controversy surrounding the exponent of 0.75 for the prediction of human drug clearance and lack of any systematic evaluation of the aforementioned proposal, the objective of this study was to determine whether the exponent 0.75 is indeed the most suitable exponent for the prediction of human drug clearance as compared to allometric scaling using the rule of exponents (ROE). Three methods were used to predict human drug clearance. Besides evaluating the exponent of 0.75, an arbitrarily selected exponent of 0.65 was also tested. ROE was also used to predict human drug clearance, and predicted values by all three methods were compared with observed human drug clearance. The results indicate that the exponent 0.75 is not the best approach for the prediction of human drug clearance. Both exponents 0.75 and 0.65 predicted human drug clearance with uncertainty, although on average the prediction of human drug clearance by 0.65 was better than the exponent 0.75. ROE provided far more accurate prediction of human drug clearance than

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either of the exponents. Although exponent 0.75 occasionally provided a good prediction of human drug clearance for a given drug for a given species, overall, the method is highly erratic and unreliable.

KEY WORDS

allometric scaling, clearance, fixed exponent 0.75, rule of exponents

INTRODUCTION

Interspecies scaling is a useful tool for the prediction of pharmacokinetic parameters from animals to humans. With the advent of new approaches, it is now possible to predict human pharmacokinetic parameters with greater accuracy than was possible 15-20 years ago. The allometric approach is based on the power function, as the pharmacokinetic parameter of interest is plotted against the body weight from several species. The power function is written as follows:

$$Y = aW^b \quad (1)$$

where Y is a parameter of interest, a is the coefficient, W is the body weight and b is the exponent of the allometry.

Equation 1 has been extensively used to predict pharmacokinetic parameters such as clearance, volume of distribution, and half-life from laboratory animals to humans. Clearance is probably the most important pharmacokinetic parameter and can be used for the selection of first-in-human dose /1,2/. Therefore, it is important that clearance be predicted in humans from animal data with as much accuracy as possible.

In 1932, Max Kleiber /3/ investigated the basal metabolic rates in several species (n = 12) and concluded that the basal metabolic rates of species are related to body size with an exponent of 0.734 (later rounded to 0.75 for ease of calculation). In later years, this theory led to the misconception that the clearance of drugs can be extrapolated across species with an exponent of 0.75, and Kleiber's exponent of 0.75 became a classic standard; any argument against it was discarded.

Huesner in 1982 /4/ suggested that the exponent 0.75 in Kleiber's equation is a statistical artifact. He pointed out that Kleiber, Brody and

others assumed that the coefficient (a) of the allometric equation ($y = aM^x$) was same for all species. He questioned the exponent 0.75 and suggested that the exponent of mass for a species is 0.67, and the coefficient of the allometric equation changes from small to large animals. Feldman and McMahon /5/ dismissed Huesner's suggestion, and using Heusner's data and by re-parameterization of his statistical model concluded that the exponent of 0.75 is a valid statistical description to describe the data on the metabolic rates of mammals.

Even today, after more than 70 years, Kleiber's exponent of 0.75 to describe interspecies allometry of metabolic rate and body mass is widely accepted. In fact, Kleiber's equation is flawed due to the lack of sufficient data. According to Hayssen and Lacy /6/, Kleiber used a very small and unrepresentative subset of animal data. Nine out of 12 species in Kleiber's data were domestic animals living under artificial energetic constraints, and there were only three primate species including human. Furthermore, it should be emphasized that clearance and basal metabolic rate are two different physiological parameters, which has not been fully grasped by the advocates of the fixed exponent of 0.75 for human drug clearance.

The exponent of 0.75 for clearance has been widely debated. Logically it is difficult to perceive that the exponent of allometry for a given parameter will revolve around a fixed number. Both the coefficients and the exponents of drug clearances widely vary and are dependent on the number of species in the scaling. Over the years, many investigators have shown that the exponent of 0.75 is not necessarily the best scaling exponent for clearance /7-11/. Nawaratne *et al.* /9/ investigated whether lean body mass correlates with hepatic and renal drug clearance. They found that the relationship between antipyrine clearance and body size had slopes ranging from 1.16 to 4.09, and the slope between creatinine clearance and body size ranged from 0.96 to 3.03. The authors suggested that the notion that drug clearance would be more accurately related to body size with an exponent of 0.75 requires further investigation.

Glazier /10/ demonstrated that the '3/4-power scaling law' of metabolic rate is not universal, either within or among animal species. Significant variation in the scaling of metabolic rate with body mass has been observed not only for animals but for unicellular organisms and plants. The author concluded that the "scaling of metabolism is not the simple result of a physical law, but rather appears to be the

more complex result of diverse adaptations evolved in the context of both physico-chemical and ecological constraints". In a recent paper, White *et al.* /10/ maintain that: "The lack of support for a single exponent model suggests that there is no universal metabolic allometry and represents a significant challenge to any model that predicts only a single value of b" (b is the allometric exponent).

In two separate studies /12,13/, Mahmood has shown that the fixed exponent of 0.75 is not the best exponent for the prediction of drug clearance in children from adult clearance. Mahmood also evaluated two arbitrary exponents, 0.80 and 0.85, to examine whether indeed exponent 0.75 predicts drug clearance in children better than two arbitrarily selected exponents. The results of the study indicated that all three exponents (0.75, 0.80, and 0.85) produced the same degree of accuracy or uncertainty in the prediction of clearance in children, suggesting that the notion that 0.75 is the most suitable allometric exponent for the prediction of clearance in children is inaccurate. There were some drugs that were predicted with comparatively more accuracy by 0.75 than 0.80 or 0.85, and vice versa. It was difficult to determine *a priori* which exponent was the most suitable for a given drug.

It must be recognized that the exponents of allometry have no physiological meaning, and the exponents of clearance for a given drug are not universal /14/. The number of species and the conditions under which a study is designed are detrimental factors for the coefficient and the exponent of allometric scaling /14/. Although there has been no systematic study to support the notion that the use of a fixed exponent of 0.75 predicts drug clearance with accuracy, the view has nevertheless been widely accepted. Taking into consideration the controversy surrounding the exponent of 0.75 for the prediction of human drug clearance, and the lack of any systematic evaluation of the aforementioned proposal, the objectives of this study were as follows:

- To determine if indeed the exponent of 0.75 is the most suitable exponent for the prediction of clearance from animals to humans;

- To compare the suitability of 0.75 with an arbitrarily selected exponent of 0.65 and the rule of exponents.

METHODS

The clearance values for 29 drugs were selected from the literature /18-68/. The total number of observations for 29 drugs was 31 because troglitazone, and metoprolol were given by both IV and oral routes. The drugs were selected based on the exponents of simple allometry and varied widely (0.286 to 1.300). The objective for the selection of drugs with exponents distant from 0.75 was to examine the suitability of 0.75 in the prediction of human drug clearance. In other words, if indeed exponent 0.75 is the most suitable exponent then it should improve the prediction of human drug clearance if the exponents of allometry are at the lower end, such as below 0.5, and at the higher end, such as ≥ 1. In order to further test the suitability of exponent 0.75, an exponent of 0.65 was arbitrarily selected.

The species used for allometric scaling and the evaluation of suitability of the exponent 0.75 or 0.65 were mouse, rat, rabbit, dog, and monkey (guinea pig was the only species for diazepam). The total number of clearance values for the fixed exponents of 0.75 or 0.65 was 116 (all animal species evaluated). At least three species were used in the allometric scaling. The following methods were used to predict clearance in humans and the predicted values were then compared with the observed human values.

Method I

The clearance in humans was predicted according to the rule of exponents as described by Mahmood /14,15/. The 'rule of exponents' incorporates the maximum lifespan potential (MLP) and 'brain weight' as correction factors in order to improve the predictive performance of allometry for the prediction of human drug clearance. The following rules were set by Mahmood and Balian /15/:

- If the exponent of simple allometry (body weight vs clearance) is within 0.55-0.70, then simple allometry should be used.
- If the exponent of simple allometry lies between 0.71 and 0.99, the MLP approach should be used.
- If the exponent of simple allometry is ≥ 1.0, brain weight is the suitable approach to predict clearance in humans compared to the other two methods.

Since the rule of exponents is not applicable to renally secreted drugs, a physiological correction factor was used as described by Mahmood /16/. For biliary excreted drugs, the rule of exponents was used in association with a physiological correction factor /16/.

Methods II-III

In these two methods, human drug clearance was predicted either by the fixed exponent of 0.75 or by an arbitrarily selected exponent 0.65. The following equation was used to predict human drug clearance:

$$\text{Predicted human drug CL} = \text{Animal CL}*(70/\text{weight of the animal})^{0\ 75/0\ 65} \quad (2)$$

where 70 is human body weight in kilograms.

Statistical analysis

Percent error between the observed and predicted values was calculated according to the following equation:

$$\%\ \text{error} = [(\text{observed} - \text{predicted})*100]/\text{observed} \quad (3)$$

The precision of the methods was measured by calculating the root mean square error (RMSE) according to the following equations:

$$\text{Mean square error (MSE)} = \Sigma(\text{predicted} - \text{observed})^2/n \quad (4)$$

$$\text{RMSE} = \sqrt{(\text{MSE})} \quad (5)$$

RMSE was expressed as percent of mean using equation 5:

$$\%\text{RMSE} = \text{RMSE}*100/\text{mean observed CL} \quad (6)$$

RESULTS

The exponents of the simple allometry in this study ranged from 0.286 to 1.300. The predicted and observed clearance values and percentage error by allometric scaling and the fixed exponent of 0.75 or 0.65 are summarized in Tables 1 and 2. The results of the study indicated that the fixed exponent of 0.75 produced substantial error in the prediction of human drug clearance as compared to allometric

scaling (at least three species) using proposed correction factors. Although a fixed exponent of 0.65 gave better prediction of human drug clearance than the exponent 0.75, the predicted values from exponent 0.65 were far more erratic than allometric scaling from three or more species (Tables 1-4). However, it should not be concluded that 0.75 should be replaced by 0.65 as a fixed exponent. Either of these values as a fixed exponent is unsuitable for the prediction of human drug clearance.

The %RMSE for Methods I-III is shown in Table 3. The %RMSE for allometric scaling was much lower than the fixed exponent of 0.75 or 0.65 against any given species. For example, the %RMSE for allometric scaling when dog was present as one of the species in allometric scaling was 23, but when dog clearance data were used for the prediction of human drug clearance using exponent 0.75 or 0.65, the %RMSE was 245 and 253, respectively. Further assessment of the suitability of the methods was done by grouping the predicted values according to percentage error (Table 4). The number of predicted errors were grouped as errors $\geq$100%, 51-99%, $\leq$50%, and <30%. For allometric scaling, there were 20 drugs out of 31 (64.5%) and 26 drugs out of 31 (83.9%) that were predicted with <30% or $\leq$50% error, respectively. On the other hand, for the exponent 0.75, there were 28 observations out of 116 (24%) and 41 out of 116 observations (35%) that were predicted with <30% or $\leq$50% error, respectively. There were only two observations which were predicted with >100% error (two were vertical allometry) by allometric scaling (6.5%), whereas there were 46 observations which were predicted with >100% error (39.6%) when the exponent 0.75 was used. There were ten observations for which the prediction error was >1,000% (8.6%) for the fixed exponent of 0.75, whereas there was only one observation for allometric scaling (diazepam) when the prediction error was >1,000% (3.2%).

The exponent 0.65 was less erratic in the prediction of human drug clearance than the exponent 0.75. There were 31 observations out of 116 (26.7%) and 57 out of 116 observations (49%) that were predicted with <30% or $\leq$50% error, respectively. The prediction error >100% was noted for 30 observations (25.9%) for the exponent 0.65 (Table 4). However, the prediction error remained substantially higher by the exponent 0.65 than by allometric scaling.

TABLE 1

Predicted and observed clearances of drugs by allometric scaling and the fixed exponent of 0.75

Drug	Obs CL	Exponents	Pred CL	Predicted CL by 0.75				
				Mouse	Rat	Rabbit	Dog	Monkey
IV administration								
Caffeine	98	0.695	110	124	223	191	92	109
% error			12	27	128	95	-6	12
Acivicin	49	0.595	51	205	89	NA	55	89
% error			4	318	82	NA	13	81
Theophylline	45	0.657	42	150	30	44	74	NA
% error			-7	234	-34	-2	65	NA
Ceftizoxime	146	0.573	128	555	330	NA	143	242
% error			-12	280	126	NA	16	89
Morphine	1100	0.684	1272	NA	1793	2068	2477	656
% error			16	NA	63	88	125	-40
Erythromycin	492	0.807	418	774	1232	1730	904	NA
% error			-15	57	150	252	84	NA
Midazolam	500	0.806	631	1092	1000	NA	1602	NA
% error			26	118	100	NA	220	NA

Drug	Obs CL	Exponents	Pred CL	Predicted CL by 0.75				
				Mouse	Rat	Rabbit	Dog	Monkey
Carumonam	96	0.773	75	157	235	159	250	146
% error			-22	64	144	66	161	52
Troglitazone	172	0.824	180	183	383	NA	288	359
% error			5	6	123	NA	68	109
Quinidine	329	0.944	297	59	582	NA	318	543
% error			-10	-82	77	NA	-3	65
Valproic acid	7	0.94	60	46	78	NA	151	124
% error			757	560	1020	NA	2057	1676
Diazepam	26	0.737	466	NA	1463	1005	996	448*
% error			1692	NA	5526	3766	3732	1622*
Metoprolol	1050	0.428	826	NA	5230	NA	1354	1178
% error			-21	NA	398	NA	29	12
Citalopram	350	0.724	455	1062	1468	NA	904	NA
% error			30	203	319	NA	158	NA
Actisomide	475	1.066	531	NA	151	NA	396	505
% error			12	NA	-68	NA	-17	6
Coumarin	1214	1.098	934	NA	291	1293	1192	796
% error			-23	NA	-76	6	-2	-34

Table 1 continued

Drug	Obs CL	Exponents	Pred CL	Predicted CL by 0.75				
				Mouse	Rat	Rabbit	Dog	Monkey
Tacrolimus	2100	1.300	2300	NA	874	940	7384	NA
% error			10	NA	-58	-55	252	NA
Oral administration								
Candoxatril	416	0.926	356	332	486	448	1467	NA
% error			-14	-20	17	8	253	NA
Troglitazone	821	0.633	793	1703	2012	NA	724	1419
% error			-3	107	145	NA	-12	73
CI-1007	26229	1.134	27113	NA	6746	NA	8033	59493
% error			3	NA	-74	NA	-69	127
Metoprolol	2763	0 286	1547	NA	18507	NA	1993	4886
% error			-44	NA	570	NA	-28	77
Ofloxacin	146	0.483	61	NA	267	NA	101	122
% error			-58	NA	83	NA	-31	-16
Enoxacin	427	0 518	286	1118	2057	NA	344	NA
% error			-33	162	382	NA	-20	NA
Indinavir	1325	0.349	872	NA	5924	NA	935	6338
% error			-34	NA	347	NA	-29	378

Drug	Obs CL	Exponents	Pred CL	Predicted CL by 0.75				
				Mouse	Rat	Rabbit	Dog	Monkey
AL01576	28.34	1.174	31.45	NA	7	NA	10	60
% error			11	NA	-77	NA	-65	113
Renally secreted								
Penem	505	0.756	527	NA	254	410	329	159
% error			4	NA	-50	-19	-35	-68
AZT	1867	0.930	1255	212	1209	NA	626	947
% error			-33	-89	-35	NA	-66	-49
Betamipron	475	0.742	498	346	307	487	345	262
% error			5	-27	-35	2	-27	-45
Biliary excreted								
Integrin antagonist	70	0.660	124	347	717	NA	238	326
% error			77	396	925	NA	240	365
Susalimod	6	0.791	11	33	308	215	72	36
% error			83	446	5034	3489	1101	503
Napsagtran	424	0.745	275	NA	1130	2293	1319	590
% error			-35	NA	166	441	211	39

All renally secreted and biliary excreted drugs were given intravenously.
* Data from guinea pig.

TABLE 2

Predicted and observed clearances of drugs by allometric scaling and the fixed exponent of 0.65

Drug				Predicted CL by 0.75				
	Obs CL	Exponents	Pred CL	Mouse	Rat	Rabbit	Dog	Monkey
IV administration								
Caffeine	98	0.695	110	57	128	137	77	84
% error			12	-42	31	39	-21	-14
Acivicin	49	0.595	51	91	51	NA	46	71
% error			4	85	3	NA	-6	44
Theophylline	45	0.657	42	66	17	33	61	NA
% error			-7	48	-62	-27	36	NA
Ceftizoxime	146	0.573	128	282	157	NA	123	190
% error			-12	93	7	NA	-16	30
Morphine	1100	0.684	1272	NA	1021	1467	2123	537
% error			16	NA	-7	33	93	-51
Erythromycin	492	0.807	418	342	701	1270	744	NA
% error			-15	-30	43	158	51	NA
Midazolam	500	0 806	631	483	563	NA	1348	NA
% error			26	-3	13	NA	170	NA

Drug				Predicted CL by 0.75				
	Obs CL	Exponents	Pred CL	Mouse	Rat	Rabbit	Dog	Monkey
Carumonam	96	0.773	75	71	132	116	211	108
% error			-22	-27	38	21	119	12
Troglitazone	172	0.824	180	83	221	NA	240	284
% error			5	-51	29	NA	39	65
Quinidine	329	0.944	297	27	331	NA	262	417
% error			-10	-92	1	NA	-20	27
Valproic acid	7	0.94	60	21	47	NA	133	97
% error			757	198	576	NA	1803	1280
Diazepam	26	0.737	466	NA	848	741	891	293*
% error			1692	NA	3161	2749	3328	1026*
Metoprolol	1050	0.428	826	NA	3032	NA	1248	954
% error			-21	NA	189	NA	19	-9
Citalopram	350	0.724	455	496	811	NA	744	NA
% error			30	42	132	NA	113	NA
Actisomide	475	1.066	531	NA	87	NA	324	393
% error			12	NA	-82	NA	-32	-17
Coumarin	1214	1.098	934	NA	174	928	1003	648
% error			-23	NA	-86	-24	-17	-47

Table 2 continued

Drug				Predicted CL by 0.75				
	Obs CL	Exponents	Pred CL	Mouse	Rat	Rabbit	Dog	Monkey
Tacrolimus	2100	1.300	2300	NA	524	702	6330	NA
% error			10	NA	-75	-67	201	NA
Oral administration								
Candoxatril	416	0.926	356	147	277	337	1208	NA
% error			-14	-65	-34	-19	190	NA
Troglitazone	821	0 633	793	787	1166	NA	599	1419
% error			-3	-4	42	NA	-27	73
CI-1007	26229	1.134	27113	NA	6746	NA	8033	59493
% error			3	NA	-74	NA	-69	127
Metoprolol	2763	0.286	1547	NA	10729	NA	1837	3957
% error			-44	NA	288	NA	-34	43
Ofloxacin	146	0.483	61	NA	155	NA	85	89
% error			-58	NA	6	NA	-42	-39
Enoxacin	427	0.518	286	515	1180	NA	283	NA
% error			-33	21	176	NA	-34	NA
Indinavir	1325	0.349	872	NA	3478	NA	770	4843
% error			-34	NA	162	NA	-42	266

Drug				Predicted CL by 0.75				
	Obs CL	Exponents	Pred CL	Mouse	Rat	Rabbit	Dog	Monkey
AL01576	28	1.174	31	NA	4	NA	8	47
% error			11	NA	-87	NA	-71	67
Renally secreted								
Penem	505	0.756	527	NA	142	283	274	120
% error			4	NA	-72	-44	-46	-76
AZT	1867	0.930	1255	212	676	NA	525	728
% error			-33	-89	-64	NA	-72	-61
Betamipron	475	0.742	498	153	178	355	284	194
% error			5	-68	-62	-25	-40	-59
Biliary excreted								
Integrin antagonist	70	0.660	124	162	411	NA	198	250
% error			77	132	488	NA	183	257
Susalimod	6	0.791	11	14	175	156	60	28
% error			83	141	2822	2496	907	363
Napsagtran	424	0.745	275	NA	646	1701	1127	459
% error			-35	NA	52	301	166	8

All renally secreted and biliary excreted drugs were given intravenously.
* Data from guinea pig.

TABLE 3

Percent root mean square error (RMSE) based on species in the prediction of human drug clearance

	No. of species	Allometry	Exp 0.75	Exp 0.65
Mouse	18	44	164	121
Rat	31	23	336	298
Rabbit	13	32	149	115
Dog	31	23	245	253
Monkey	23	22	419	247

DISCUSSION

The notion of a fixed exponent of 0.75 in the prediction of human drug clearance comes from Kleiber's original work relating basal metabolic rate against body weight across several species. The advocates of a fixed exponent of 0.75 in the prediction of human drug clearance fail to recognize that drug clearance in animals and humans and basal metabolic rate are two different physiological terms and are not related to each other. Furthermore, based on the available data. it is obvious that the exponents of allometry vary widely and do not revolve around 0.75. Of course, for some drugs (depending on the species in the scaling) the exponents of allometry for clearance may be 0.75 or close to it, but simple logic dictates that the use of a fixed exponent of 0.75 for each and every drug is illogical. A systematic evaluation of exponent 0.75, to determine whether indeed this is the most suitable exponent to predict human drug clearance, has not been performed. The current study not only evaluates the predictive performance of a fixed exponent of 0.75 but also evaluates an arbitrarily selected exponent of 0.65.

One should recognize that the exponents of allometry have no physiological meaning /14/. The exponents of clearance for a given drug are not universal and will vary depending on the species and sample size used in the allometric scaling /14/. Due to the very nature of the exponents of allometry, it is not surprising that a fixed single exponent does not predict human drug clearance as accurately as three or more species allometric scaling. Therefore, the notion that 0.75 is

TABLE 4

Number of species based on percentage error for the prediction of human drug clearance

Species	Exponents	≤30	≤50	51-99	≥100
Mouse (n = 18)	0.75	4	4	4	10
Mouse (n = 18)	0 65	5	8	6	4
Allometry (n = 18)	NA	11	14	2	1
Rat (n = 31)	0 75	1	7	8	16
Rat (n = 31)	0.65	7	12	10	9
Allometry (n = 31)	NA	19	25	3	2
Rabbit (n = 13)	0.75	5	5	4	4
Rabbit (n = 13)	0.65	5	8	1	4
Allometry (n = 13)	NA	9	11	1	1
Dog (n = 31)	0.75	13	15	6	10
Dog (n = 31)	0.65	8	17	4	10
Allometry (n = 31)	NA	19	25	3	2
Monkey (n = 23)	0.75	5	10	7	6
Monkey (n = 23)	0.65	6	12	7	4
Allometry (n = 23)	NA	15	19	3	1

NA = not applicable.

the best exponent for the prediction of human drug clearance is inaccurate.

The exponent 0.65 appears to predict human drug clearance slightly better than 0.75. For most of the drugs and in most species in Table 2 the exponent 0.65 predicted human drug clearance better than

the exponent 0.75. However, it is difficult to determine *a priori* which exponent (0.65 or 0.75) is suitable for a given drug.

Hu and Hayton /17/, by statistical analysis and Monte Carlo simulation, attempted to characterize uncertainty in the allometric exponent (b) of xenobiotic clearance. The main objective of their study was to determine whether the allometric exponent 0.75 was universal and whether it differed from exponent 0.67. The authors used 115 compounds in their evaluation. The mean ± standard deviation of the b values was 0.74 ± 0.16 (range: 0.29-1.2). The authors concluded that their results supported the possibility of the existence of a universal b value, and the range of values (0.29-1.2) seen was due to random error in clearance determination. The authors also found that the mean b value of 0.65 for renally excreted drugs was statistically different from exponent 0.75 but not 0.67. Based on 95% and 99% confidence intervals (CI), the authors also found that individual b values did not differ from 0.67 or 0.75. This study by Hu and Hayton may be statistically sound, but one cannot ignore the reality and practical aspects of allometric scaling for the prediction of human drug clearance from animal data. For both 95% and 99% CI, the range was so wide that most of the drugs fell into the range of these CI. Based on such a wide CI, an exponent of 0.95 obtained from the allometric scaling of three or more species may not be different from a mean exponent of 0.75, yet for practical purposes these two exponents are different and will have enormous impact on the prediction of human drug clearance (as seen in this paper). The reality is that for pharmacokinetic allometric scaling, data from only three to four species will be available, and one has to utilize these limited data for the prediction of human pharmacokinetic parameters. Therefore, the statistical significance or insignificance for b has no practical value, and the exponent of allometry should be determined for each and every drug, and that exponent should be used for the prediction of human drug clearance.

The data in Tables 1-4 provide some insights into the inappropriateness and random nature of the fixed exponent 0.75 for the prediction of human drug clearance:

- Occasionally, for some drugs, good or acceptable predictions (with acceptable error) were obtained using the exponent 0.75. Such predictions were, however, species dependent. For example, theophylline clearance was predicted with reasonable accuracy from rat

(34% prediction error) and rabbit (2% prediction error), but prediction from dog (65% prediction error) and mouse (234% prediction error) data was erratic. The prediction error of theophylline was 7% by allometric scaling. Another such example of the inappropriateness of the use of 0.75 is ceftizoxime. Ceftizoxime clearance was predicted with accuracy from dog (16% prediction error) but prediction from mouse (280% prediction error), rat (126% prediction error) and monkey (89% prediction error) data was highly erratic. The prediction error of ceftizoxime was 12% by allometric scaling. Overall, this kind of observation was noted for all drugs.

- Although occasionally for a given drug one may get an accurate prediction of human drug clearance from a given species by exponent 0.75, it is difficult to determine *a priori* which species is a suitable species to provide a reasonable prediction. For example, for indinavir, the predicted human drug clearance was 29% from dog but over 300% from rat and monkey. Thus, the randomness of the exponent 0.75 in the prediction of human drug clearance is obvious.

- Diazepam is a drug which follows the concept of vertical allometry. The exponent of allometry for diazepam using rat, guinea pig, rabbit, and dog was 0.737. However, the application of 0.75 on individual species gave prediction errors of 5,526% (rat), 1,622% (guinea pig), 3,766% (rabbit), and 3,732% (dog). The error in the predicted clearance of diazepam in humans by allometric scaling was 1,692%. This further provides evidence that 0.75 is not a suitable exponent for individual species.

- In the current analysis, besides diazepam, three other drugs, penem (exponent 0.756), betamipron (exponent 0.742), and napsagtran (exponent 0.745), were very close to 0.75, yet the prediction error varied widely. For example, the variability in the prediction error of penem (from 19-68%; prediction error from allometry 4%), betamipron (from 2-45%; prediction error from allometry 5%), and napsagtran (from 39-441%; prediction error from allometry 35%) was fairly wide. Had 0.75 been the most suitable exponent, then one should have obtained a fairly good prediction at least for these drugs from any species, but this was not the case.

- For those drugs whose allometric exponent was ≤0.5 or ≥1.0, the prediction error using exponent 0.75 remained erratic. A given species predicted the clearance of these drugs fairly well but the prediction error varied widely from species to species leading to uncertainty in the prediction.
- The prediction of human drug clearance by an arbitrarily selected exponent of 0.65 (for most of the drugs across species) was comparatively better than the exponent 0.75. This clearly demonstrates that 0.75 is as arbitrary as 0.65. However, one should not assume that 0.75 should be replaced by 0.65 as a fixed exponent.
- On average, no single species provided better prediction than allometric scaling when the exponent 0.75 or 0.65 was applied. The prediction error was substantial for any one species evaluated in this study when the exponent 0.75 or 0.65 was used.

CONCLUSIONS

The current analysis demonstrates that there is no role for a fixed exponent in allometric scaling for the prediction of human drug clearance. Occasionally one may get a fairly good prediction of human drug clearance for a given drug from a species using a fixed exponent (0.75 or 0.65), but it is difficult to determine *a priori* which one is a suitable species. An appropriate approach is the use of the exponent obtained from the allometric scaling of ≥3 species for a given drug. It should be noted, however, that for the same drug, the exponent of allometry will vary depending on the number of species used in the scaling.. In the light of the current study and two previous studies conducted by Mahmood /12,13/, the use of the fixed exponent 0.75 should also be discouraged to predict drug clearance in children from adult data. In the case of children, an allometric model for clearance within a given age group (neonates and infants, children, older children, or adolescents) should be developed for each and every drug /69/.

REFERENCES

1. Mahmood I, Green MD, Fisher JE. Selection of the first-time dose in humans: comparison of different approaches based on interspecies scaling of clearance. J Clin Pharmacol 2003; 43: 692-697.
2. Mahmood I. First-in-human dose selection. In: Interspecies Pharmacokinetic Scaling: Principles and Application of Allometric Scaling. Rockville, MD: Pine House Publishers, 2005; 259-287.
3. Kleiber M. Body size and metabolism. Hilgardia 1932; 6: 315.
4. Heusner AA. Energy metabolism and body size I. Is the 0.75 mass exponent of Kleiber's equation a statistical artifact? Resp Physiol 1982; 48: 13-25.
5. Feldman HA, McMahon TA. The 3/4 mass exponent for energy metabolism is not a statistical artifact? Resp Physiol 1983; 52: 149-163.
6. Hayssen V, Lacy RC. Basal metabolic rates in mammals: taxonomic differences in the allometry of BMR and body mass. Comp Biochem Physiol A 1985; 81: 741-754.
7. Mahmood I. On the exponents of allometry. In: Interspecies Pharmacokinetic Scaling. Principles and Application of Allometric Scaling. Rockville, MD: Pine House Publishers, 2005; 86-90.
8. Taylor CR, Maloiy GM, Weibel ER, Langman VA, Kamau JM, et al. Design of the mammalian respiratory system III. Scaling maximum aerobic capacity to body mass: wild and domestic mammals. Resp Physiol 1981; 44: 25-37.
9. Nawaratne S, Brien JE, Seeman E, Fabiny R, Zalcberg J, et al. Relationships among liver and kidney volumes, lean body mass and drug clearance. Br J Clin Pharmacol 1998; 46: 447-452.
10. Glazier DS. Beyond the '3/4-power law': variation in the intra- and inter-specific scaling of metabolic rate in animals. Biol Rev Camb Philos Soc 2005; 80: 611-662.
11. White CR, Cassey P, Blackburn TM. Allometric exponents do not support a universal metabolic allometry. Ecology 2007; 88: 315-323.
12. Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol 2006; 61: 545-557.
13. Mahmood I. Prediction of drug clearance in children: impact of allometric exponents, body weight and age. Ther Drug Monit 2007; 29: 271-278.
14. Mahmood I. Interspecies scaling of clearance. In: Interspecies Pharmacokinetic Scaling. Principles and Application of Allometric Scaling. Rockville, MD: Pine House Publishers, 2005; 39-85.
15. Mahmood I, Balian JD. Interspecies scaling: predicting clearance of drugs in humans: three different approaches. Xenobiotica 1996; 26: 887-895.
16. Mahmood I. Interspecies scaling of drugs cleared by the kidneys and the bile. In: Interspecies Pharmacokinetic Scaling. Principles and Application of Allometric Scaling. Rockville, MD: Pine House Publishers, 2005; 105-143.
17. Hu TM, Hayton WL. Allometric scaling of xenobiotic clearance: uncertainty versus universality. AAPS PharmSci 2001; 3: E29.

18. Bonati M, Latini R, Tognoni G. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. Drug Metab Rev 1984-85; 15: 1355-1383.
19. Boothe DM, Cullen JM, Calvin JA, Jenkins WL, Brown SA, Green RA, Corrier DE. Antipyrine and caffeine dispositions in clinically normal dogs and dogs with progressive liver disease. Am J Vet Res 1994; 55: 254-261.
20. McGovren JP, Williams MG, Stewart JC. Interspecies comparison of acivicin pharmacokinetics. Drug Metab Dispos 1988; 16: 18-22.
21. Gascon RA, Calvo B, Hernandez RM, Dominguez-Gil A, Pedraz J. Interspecies scaling of cimetidine-theophylline pharmacokinetic interaction: interspecies scaling in pharmacokinetic interaction. Pharm Res 1994; 11: 945-950.
22. Chiou WL, Choi YM. Unbound total (plasma) clearance approach in interspecies pharmacokinetics correlation: theophylline-cimetidine interaction. Pharm Res 1995; 12: 1238-1239.
23. Gaspari F, Bonati M. Interspecies metabolism and pharmacokinetic scaling of theophylline disposition. Drug Metab Rev 1990; 22: 179-207.
24. Murakawa T, Sakamoto H, Fukada S, Nakamoto S, Hirose T, Itoh N, Nishida M. Pharmacokinetics of ceftizoxime in animals after parenteral dosing. Antimicrob Agents Chemother 1980; 17: 157-164.
25. Nakashima N, Suzuki K, Hashimoto H, Nishijima K. Phase I study of ceftizoxime, a new cephalosporin. Single-dose study. J Clin Pharmacol 1981; 21: 388-395.
26. Miline RW, Nation RL, Somogyi A. The disposition of morphine and its 3- and 6-glucuronide metabolites in humans and animals, and the importance of the metabolites to the pharmacological effects of morphine. Drug Metab Rev 1996; 28: 345-472.
27. Duthu GS. Interspecies correlation of the pharmacokinetics of erythromycin, oleandomycin, and tylosin. J Pharm Sci 1985; 74: 943-946.
28. Mandema JW, Tukker E, Danhof M. Pharmacokinetic-pharmacodynamic modelling of the EEG effects of midazolam in individual rats: influence of rate and route of administration. Br J Pharmacol 1991; 102: 663-668.
29. Granvil CP, Yu AM, Elizondo G, Akiyama TE, Cheung C, Feigenbaum L, Krausz KW, Gonzalez FJ. Expression of the human CYP3A4 gene in the small intestine of transgenic mice: in vitro metabolism and pharmacokinetics of midazolam. Drug Metab Dispos 2003; 31: 548-558.
30. Kuroha M, Azumano A, Kuze Y, Shimoda M, Kokue E. Effect of multiple dosing of ketoconazole on pharmacokinetics of midazolam, a cytochrome P-450 3A substrate in beagle dogs. Drug Metab Dispos 2002; 30: 63-68.
31. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet 1989; 16: 337-364.
32. Kita Y, Fugono T, Imada A. Comparative pharmacokinetics of carumonam and aztreonam in mice, rats, rabbits, dogs, and cynomolgus monkeys. Antimicrob Agents Chemother 1986; 29: 127-134.
33. Berube D, Vallee F, Panneton A-C, Bergeron MG, Lebel M. Pharmacokinetics of carumonam after single and multiple 1- and 2-g dosage regimens. Antimicrob Agents Chemother 1988; 32: 354-357.

34. Izumi T, Enomoto S, Hosiyama K, Sasahara K, Shibukawa A, Nakagawa T, Sugiyama Y. Prediction of the human pharmacokinetics of troglitazone, a new and extensively metabolized antidiabetic agent, after oral administration, with an animal scale-up approach. J Pharmacol Exp Ther 1996; 277: 1630-1641.
35. Loi CM, Young M, Randinitis E, Vassos A, Koup JR. Clinical pharmacokinetics of troglitazone. Clin Pharmacokinet 1999; 37: 91-104.
36. Guentert TW, Huang JD, Qie S. Disposition of quinidine in the rabbit. J Pharm Sci 1982; 71: 812-815.
37. Iven H. The pharmacokinetics and organ distribution of ajmaline and quinidine in the mouse. Naumyn-Schmiedbergs Arch Pharmacol 1977; 298: 43-50.
38. Ueda CT, Ballard BE, Rowland M. Concentration-time effects on quinidine disposition kinetics in rhesus monkeys. J Pharmacol Exp Ther 1977; 200: 459-468.
39. Loscher W. Serum protein binding and pharmacokinetics of valproate in man, dog, rat and mouse. J Pharmacol Exp Ther 1978; 204: 255-261.
40. Lai AA, Levy RH, Martis L. Pharmacokinetic profile of valproic acid in rhesus monkeys following single bolus and constant rate intravenous administrations. Therapie 1980; 35: 221-232.
41. Klotz U, Antonin KH, Bieck PR. Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig and rat. J Pharmacol Exp Ther 1976; 199: 67-73.
42. Rane A, Hogstedt S, Lindberg B, Regardh CG, Jorulf H. Comparison of different clearance estimates for metoprolol in the rhesus monkey. J Pharmacol Exp Ther 1984; 228: 774-778.
43. Belpaire FM, Smet FD, Vynckier LJ, Vermeulen AM, Rosseel MT, Bogaert MG, Moachon-Chauvelot L. Effect of aging on the pharmacokinetics of metoprolol and propranolol in the rat. J Pharmacol Exp Ther 1990; 254: 116-122.
44. Murthy SS, Nelson WL, Shen DD, Power JM, Cahill CM, McClean AJ. Pharmacokinetic interaction between verapamil and metoprolol in the dog. Stereochemical aspects. Drug Metab Dispos 1991; 19: 1093-1100.
45. Bortolotti A, Castelli D, Verotta D, Bonati M. Pharmacokinetic and pharmacodynamic modeling of metoprolol in rabbits with liver failure. Eur J Drug Metab Pharmacokinet 1989; 14: 145-151.
46. Fredricson Overø K. Kinetics of citalopram in test animals; drug exposure in safety studies. Prog Neuropsychopharmacol Biol Psychiatry 1982; 6: 297-309.
47. Cook CS, Rozek LF, Stolzenbach J, Anderson S, Schoenhard GL, Karim A. Pharmacokinetics of a novel antiarrhythmic drug, actisomide. Pharm Res 1993; 10: 427-433.
48. Ritschel WA, Vachharajani NN, Johnson RD, Hussain AS. Interspecies scaling of the pharmacokinetic parameters of coumarin among six different mammalian species. Methods Find Exp Clin Pharmacol 1991; 13: 697-702.
49. Riekosezewski W, Chow FS, Jusko WI. Disposition of tacrolimus (FK 506) in rabbits. Role of red blood cell binding in hepatic clearance. Drug Metab Dispos 1993; 21: 690-698.

50. Takada K, Usuda H, Ohhashi, M, Yoshikawa H. Muranishi S, Tanaka H. Pharmacokinetics of FK-506, a novel immunosuppressant, after intravenous and oral administration to rats. J Pharmacobiodyn 1991; 14: 34-42.
51. Venkataramanan R, Cadoff JE, Warty V, Iwasaki K, Nagase K, Krajack A, Imventarza O, Todo S, Fung J, Starzl TE. Pharmacokinetics of FK-506: preclinical and clinical studies. Transplant Proc 1990; 22 (Suppl 1): 52-56.
52. Venkataramanan R, Swaminathan A, Prasad T, Jain A, Zuckerman S, Warty V, McMichael J, Lever J, Burckart G, Starzl T. Clinical pharmacokinetics of tacrolimus. Clin Pharmacokinet 1995; 29: 404-430.
53. Kaye B, Brearley CJ, Cussans NJ, Herron M, Humphrey MJ, Mollat AR. Formation and pharmacokinetics of the active drug candoxatrilat in mouse, rat, rabbit, dog and man following administration of the prodrug candoxatril. Xenobiotica 1997; 27: 1091-1102.
54. Feng MR, Loo J, Wright J. Disposition of the antipsychotic agent CI-I007 in rats, monkeys, dogs, and human cytochrome P450 2D6 extensive metabolizers. Species comparison and allometric scaling. Drug Metab Dispos 1998; 26: 982-988.
55. Kawakaini J, Yamamoto K, Swada Y, Iga T. Prediction of brain delivery of ofloxacin, a new quinolone, in the human from animal data. J Pharmacokinet Biopharm 1994; 22: 207-227.
56. Nakamura S, Kurobe N, Kashimoto S, Ohue T, Takase Y, Shimizu M. Pharmacokinetics of AT-266 administered orally to mice, rats, dogs and monkeys. Antimicrob Agents Chemother 1983; 24: 54-60.
57. Somogyi AA, Bochner F. The absorption and disposition of enoxacin in healthy subjects. J Clin Pharmacol 1988, 28 707-713.
58. Lin JH, Chiba M, Balani SK, Chen I-WU, Kwei G, Vastag KJ, Nishime JA. Species differences in the pharmacokinetics and metabolism of indinavir, a potent human immunodeficiency virus protease inhibitor. Drug Metab Dispos 1996; 24: 1111-1120.
59. Balani SK, Woolf EJ, Hoagland VL, Sturgill MG, Deutsch PI, Yeh KC, Lin JH. Disposition of indinavir, a potent HIV-I protease inhibitor, after an oral dose in humans. Drug Metab Dispos 1996; 24 1389-1392.
60. Brazell RK, Pask YH, Wooldridge CB, McCue B, Basker R, Couch R, York B. Interspecies comparison of the pharmacokinetics of aldose reductase inhibitors. Drug Metab Dispos 1990; 18: 435-440.
61. Efthymiopoulos C, Battaglia R, Strolin Benedetti M. Animal pharmacokinetics and interspecies scaling of FCE 22101, a penem antibiotic. J Antimicrob Chemother 1991; 4: 517-526.
62. Jannuzzo MG, Mandelli M, Benedetti MS, Moro E, Carnovali M, Vaiani R, Sassella D. Pharmacokinetics and tolerance of a new penem antibiotic, FCE 22101, in healthy volunteers after a single intravenous dose. Eur J Clin Pharmacol 1989; 36: 633-635.
63. Patel BA, Boudinot FD, Schinazi RF, Gallo JM, Chu CK. Comparative pharmacokinetics and interspecies scaling of 3′-azido-3′-deoxythymidine (AZT) in several mammalian species. J Pharmacobiodyn 1990; 13: 206-211.

64. Kurihara A, Naganuma H, Hisaoka M, Tokiwa H, Kawahara Y. Prediction of human pharmacokinetics of panipenem-betamipron, a new carbapenem, from animal data. Antimicrob Agents Chemother 1992; 36: 1810-1816.
65. Cui D, Subramanian R, Shou M, Yu X, Wallace MA, Braun MP, Arison BH, Yergey JA, Prueksaritanont T. In vitro and in vivo metabolism of a potent and selective integrin $\alpha_v\beta_3$ antagonist in rats, dogs, and monkeys. Drug Metab Dispos 2004; 32: 848-861.
66. Prueksaritanont T, Fernandez-Metzler C, Meng Y, Barrish A, Halczenko W, Rodan SB, Hutchinson JH, Duggan ME, Lin JH. Disposition of a novel and potent $\alpha_v\beta_3$ antagonist in animals, and extrapolation to man. Xenobiotica 2004; 34: 103-115.
67. Pahlman I, Edholm M, Kankaanranta S, Odell M-L. Pharmacokinetics of susalimod, a highly biliary-excreted sulphasalazine analogue, in various species. Nonpredictable human clearance by allometric scaling. Pharm Pharmacol Commun 1998; 4: 494-498.
68. Lave T, Portmann R, Schenker Gianni, Guenz A., Girometta M-A., Schmitt M. Interspecies pharmacokinetic comparisons and allometric scaling of napsagatran, a low moecular weight thrombin inhibitor. J Pharm Pharmacol 1999; 51: 85-91.
69. Mahmood I. Prediction of pharmacokinetic parameters in children: application of allometric principles. In: Pediatric Pharmacology and Pharmacokinetics. Rockville, MD: Pine House Publishers, 2008; 142-183.